ORIGINAL ARTICLES

Prevalence of abnormal serum aminotransferase values in overweight and obese adolescents

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Objectives: (1) To determine the prevalence of abnormal liver enzymes in overweight and obese adolescents and (2) to determine the relationship of alcohol ingestion and serum antioxidants to the presence of abnormal liver enzymes in overweight and obese adolescents.

Methods: Serum alanine aminotransferase (ALT) and γ-glutamyl transpeptidase levels were measured in 2450 children between the ages of 12 and 18 years, enrolled in the National Health and Examination Survey, cycle III (NHANES III). Obesity was defined as a body mass index >95th percentile for age and sex. Overweight was defined as a body mass index >85th percentile for age and sex. Nutritional intake was assessed by 24-hour dietary recall and food frequency questionnaires. Serum antioxidants were measured by high-pressure liquid chromatography.

Results: Sixty percent of adolescents with elevated ALT levels were either overweight or obese. Overall, 6% of overweight adolescents had elevated ALT levels (odds ratio: 3.4 [95% CI: 3.5-12.8]). Ten percent of obese adolescents had elevated ALT levels (odds ratio: 6.7 [95% CI: 3.5-12.8]). In addition, approximately 1% of obese adolescents demonstrated ALT levels over twice normal. Approximately 50% of of obsese adolescents who reported modest alcohol ingestion (4 times per month or more) had elevated ALT levels (odds ratio: 10.8, 95% CI: 1.5-77). Other factors associated with elevated ALT levels in overweight and obese adolescents include increased age, elevated glycolated hemoglobin, elevated triglycerides, and decreased levels of serum antioxidants—vitamin E, β-carotene, and vitamin C.

Conclusion: Overweight and obesity are the most common findings in adolescents with elevated ALT levels. Even modest alcohol consumption may significantly increase the likelihood of obese adolescents developing obesity-related liver disease. (J Pediatr 2000;136:727-33)

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Nonalcoholic steatohepatitis is a common cause of chronic liver disease in obese adults. Autopsy studies suggest that approximately 19% of obese adults have evidence of NASH.[1] Other studies suggest that up to 60% to 70% of obese adults have evidence of steatosis on liver biopsy, and approximately 20% have evidence of active inflammation and fibrosis.[2-4]

See related articles, p. 711, p. 734, and p. 739.

The prevalence of NASH among obese adolescents is unknown. Moran et al[5] first demonstrated severe hepatitis and fibrosis in 3 children aged 10 to 13 years.[5] Baldridge et al[6] also described severe changes of steatohepatitis associated with portal inflammation and portal fibrosis in 14 obese children. In addition, Kinugasa et al[7] described the presence of significant steatohepatitis in 8 of 11 obese Japanese children who underwent liver biopsy for elevated liver enzymes. With the use of hepatic ultrasonography, Tominaga et al[8] found fatty changes in approximately 22% of obese boys and girls aged 4 to 12 years old.[8] Unfortunately, serum aminotransferases were not measured.

ALT	Serum alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
GGTP	Serum γ-glutamyl transpeptidase
NASH	Nonalcoholic steatohepatitis
NHANES III	National Health and Nutrition Examination Survey, cycle III

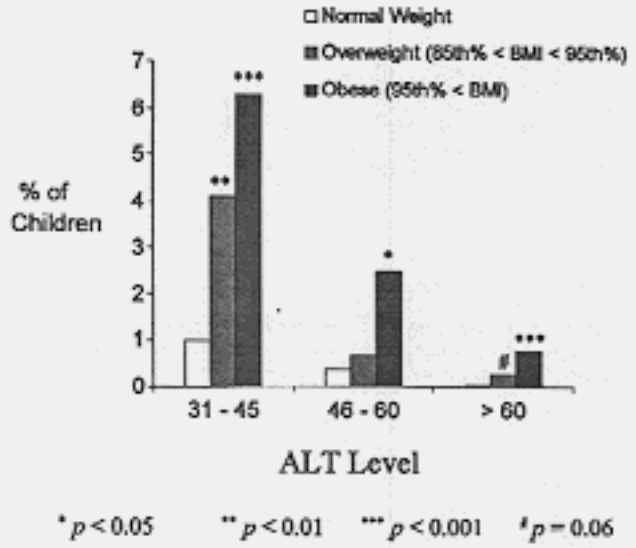

Fig 1. Degree of ALT elevations in normal weight, overweight, and obese children. Mild ALT elevations (1 to 1.5x normal) were significantly more common in both overweight ($P < .01$) and obese ($P < .001$) adolescents than in normal weight adolescents. However, only obese adolescents had ALT elevations 1.5 to 2x normal ($P < .05$) and greater than 2 times normal ($P < .001$). A similar trend was also observed for ALT levels greater than 2 times normal in overweight adolescents ($P = .06$).

Table I. Characteristics of children enrolled in NHANES III, 1988-1994

	Normal weight: BMI <85th% (n = 1729)	Overweight: 85th% < BMI < 95th% (n = 411)	Obese: BMI >95th% (n = 332)
Sex (% male)	51	48	55
Age (y)	15.1 ± 0.1	14.7 ± 0.1	14.9 ± 0.1
Weight (kg)	55.5 ± 0.2	69.6 ± 0.7*	90.1 ± 1.5*
Height (cm)	165.7 ± 0.2	165.0 ± 0.6	166.3 ± 0.6
BMI (% median)	1.02 ± 0.01	1.30 ± 0.01*	1.64 ± 0.02*
Race			
White/Hispanic (%)	80	82	78
Black (%)	15	16	21*
Other (%)	5	2	1†
Alcohol ingestion			
<4×/mo (%)	91.3	95.1	93.2
≥4×/mo (%)	8.7	5.9	6.8

Age, weight, height, and BMI are expressed as mean ± SEM.
Differences in proportions were assessed with χ^2 analysis. Differences in continuous variables were determined with 1-way analysis of variance. Children without ALT measurements and children with evidence of hepatitis B or C were excluded.
*$P < .001$ compared with other groups.
†$P < .05$ compared with other groups.

To address the influence of childhood obesity on the prevalence of liver enzyme abnormalities in a large cross-sectional sample of American children, data were analyzed from the National Health and Nutrition Examination Survey, cycle III, a nationally representative sample of children and adults that was conducted from 1988 through 1994. Comprehensive data including race, weight, height, nutritional intake, and serum antioxidants allowed for analysis of physiologic influences on the serum liver test results of overweight and normal weight children.

METHODS

Sample

NHANES III, the seventh in a series of large national health examination surveys conducted in the United States since the 1960s, examined a nationally representative sample of children and adults between 1988 and 1994. The sample included 2450 children, ages 12 through 18 years, with liver enzyme measurements (86% of NHANES III adolescent cohort). Weights and heights were available for >99% of the children.

Anthropometrics

Body weight and height were measured according to previously described methods.[9] Reference body mass index percentiles were derived from the first NHANES.[10] This definition is in accordance with recommendations of the Expert Committee on Clinical Guidelines for Overweight in Adolescence[11] and Expert Committee on Obesity Evaluation and Treatment.[12] Normal weight was defined as a BMI (kg/m^2) <85th percentile for age and sex. We classified adolescents with a BMI (kg/m^2) >85th percentile for age and sex as *overweight* and those with a BMI (kg/m^2) >95th percentile for age and sex as *obese*.[11,12] For the purposes of this study, "adolescents" were defined as 12- to 18-year-old children.

Nutritional Assessment

Nutritional intake was assessed with a food frequency questionnaire and 24-hour diet recall. The food frequency questionnaire included an assessment of alcohol intake. Previous studies have demonstrated the validity and reliability of reported adolescent alcohol intake.[13-15] Intake of fat, energy, and protein were calculated with the United States Department of Agriculture's Survey Nutrient Data Base based on

Table II. Percent of adolescents with abnormal liver enzymes in NHANES III, 1988-1994

	Normal weight	Overweight (85 < BMI < 95th%)	Obese (BMI > 95th%)
All children			
ALT >normal (30 U/L)	1.5% (n = 1737)	5.0% (n = 413)*	9.5% (n = 334)*
GGTP > normal (35 U/L)	1.2% (n = 1342)	1.3% (n = 326)	3.9% (n = 271)†
Alcohol <4×/mo			
ALT >normal (30 U/L)	1.7% (n = 1597)	5.3%* (n = 392)	5.9%* (n = 313)
GGTP >normal (35 U/L)	1.2% (n = 1245)	1.3% (n = 314)	4.0%* (n = 253)
Alcohol ≥4×/mo			
ALT >normal (30 U/L)	0.2% (n = 140)‡	0.6% (n = 21)‡	52.2%† (n = 21)
GGTP >normal (35 U/L)	0.8% (n = 97)‡	2.8% (n = 12)‡	2.9% (n = 18)‡

*$P < .001$ compared with normal weight.
†$P < .01$ compared with normal weight.
‡Potentially unstable estimates caused by relatively large standard error.

the 24-hour dietary recall that the adolescents provided themselves. Interviews were conducted privately by trained study staff, and staff performance was monitored routinely.

Laboratory Testing

Serum alanine aminotransferase was measured in 2450 children (86%), and serum γ-glutamyl transpeptidase was measured in 1914 (67%). Serum levels of glucose, cholesterol, triglycerides, and glycated hemoglobin were measured with standardized instruments. Fasting levels (>6 hours) were obtained in approximately 80% of adolescents. Serum levels of antioxidants were measured according to previously described methods.[16] Children with positive test results for hepatitis B core antibody, hepatitis B surface antigen, and hepatitis C antibody were excluded from the statistical analysis. One normal weight adolescent with elevated transferrin saturation (>50%), serum ferritin (>90th percentile), and GGTP was also excluded. Abnormal ALT levels were defined as >30 U/L, abnormal aspartate aminotransferase values were defined as >35 U/L, and abnormal GGTP levels were defined as >35 U/L.[17] These cutoff values correspond to approximately the 97th to 98th percentile of the NHANES III adolescent population and are similar to cutoff values used in other studies.[7,8]

Table III. Odds ratios for elevated liver enzymes in NHANES III, 1988-1994

	Odds ratio (95% CI)	
	Overweight vs normal weight	Obese vs normal weight
All adolescents		
ALT >normal (30 U/L)	3.4 (1.7-6.8)	6.7 (3.5-12.8)
GGTP >normal (35 U/L)	1.1 (0.6-1.9)	3.3 (1.9-5.7)
Alcohol <4×/mo		
ALT >normal (30 U/L)	3.3 (1.7-6.6)	3.8 (2.0-6.9)
GGTP >normal (35 U/L)	1.0 (0.6-1.9)	3.3 (1.9-5.8)
Alcohol ≥4×/mo		
ALT >normal (30 U/L)	3.1 (0.3-37)	...*
GGTP >normal (35 U/L)	3.4 (0.6-21)	3.6 (0.6-22)

*Unstable estimate caused by small number of normal weight adolescents who consumed alcohol ≥4×/mo and had elevated ALT levels (ie, odds ratio: 600 [72 to 5000]).

Statistics

The NHANES III study oversampled blacks, younger children, and the elderly. With the use of sample weights provided by NHANES III, the data were adjusted to account for unequal selection. To adjust for complex sample design and clustering effects in the NHANES III sample, statistical significance was assessed with the balanced repeated replication method with the software package WesVarPC (Westat Inc, Rockville, Md) as recommended.[18] The balanced repeated replication method provides for a general means of estimating variance in clustered, multistrata surveys such as NHANES III while adjusting for the effects of nonresponse and poststratification.[18]

Differences in proportions were assessed with χ^2 analysis. Odds ratios were calculated with logistic regression analysis. To provide enough power to detect significant differences in antioxidants, serum lipids, glycolat-

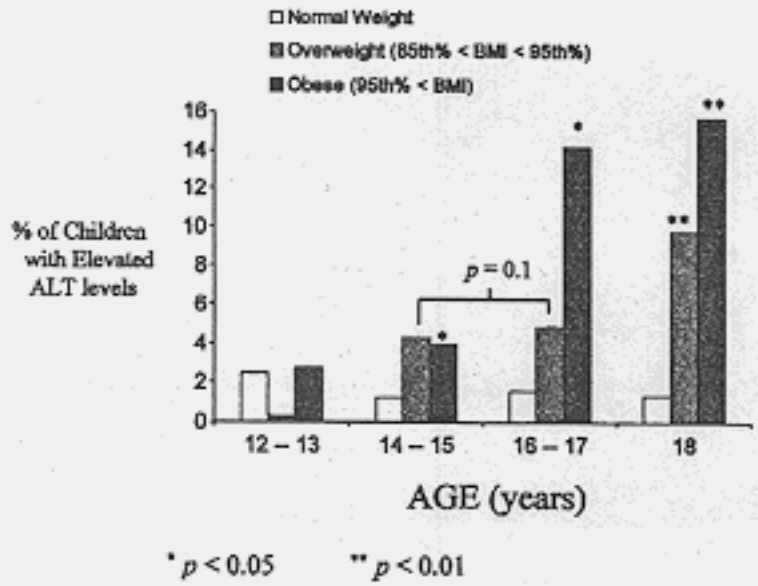

Fig 2. Percentage of children with elevated ALT levels by age. Increased prevalence of elevated ALT levels was demonstrated for each age group of obese adolescents. Increased prevalence of elevated ALT levels was observed in 18-year-old overweight children. A similar trend was also observed in 14- to 17-year-old overweight adolescents ($P = .1$).

ed hemoglobin, and dietary intake of children with or without abnormal ALT levels, data from overweight and obese children were combined (BMI >85th percentile). Multivariate logistic regression analysis was used to assess the independent effects of dietary intake, serum antioxidants, serum lipids, and glycated hemoglobin on the prevalence of abnormal ALT levels in overweight and obese children.

RESULTS

Approximately 16% of adolescents were overweight (85th percentile < BMI <95th percentile), and 10% were obese (BMI >95th percentile). Similar results were previously reported for the 1988 to 1991 adolescent subgroup of NHANES III.[19] Minimal differences in sex, age, height, and alcohol consumption existed between normal weight, overweight, and obese children. Obese children were more likely to be black than were overweight or normal weight children ($P < .001$) (Table I).

Abnormal serum ALT levels were found in 79 children. Four of these children had evidence of hepatitis B or C infections and were excluded from further analysis (2 normal weight adolescents with hepatitis B core antibody and surface antigen; 1 overweight and 1 obese adolescent with hepatitis C antibody). Of the remaining 75 children with elevations in serum ALT, 61% were overweight or obese. Of 35 children with isolated elevations in GGTP, 45% were overweight or obese. Overall, overweight children were significantly more likely to have abnormal ALT levels compared with normal weight children (Tables II and III). Obese children were also significantly more likely to have abnormal ALT levels compared with normal weight children (Tables II and III). In addition, obese children were significantly more likely to have higher levels of ALT than were overweight or normal weight children (Fig 1); 0.8% of obese children had ALT levels >60 compared with 0.06% of normal weight children ($P < .001$, odds ratio 12.3, 95% CI, 4.2 to 36). Obese children also had elevations in serum GGTP compared with normal weight children ($P < .01$). Overall, 58% of children with elevated ALT levels also had elevated AST levels, and 54% of children with elevated ALT levels also had elevated GGTP levels.

The prevalence of abnormal ALT levels did not differ for overweight black and white adolescents ($P = .5$) or for obese black and white adolescents ($P = .8$). The prevalence of abnormal ALT levels was significantly higher among overweight boys compared with overweight girls (7.9% vs 2.3%, $P < .01$). However, there was no difference in abnormal ALT levels for obese boys and obese girls (10.8% vs 7.8%, $P = .4$). Overweight and obese adolescents older than 16 years were particularly likely to have abnormal ALT levels (Fig 2).

Influence of Alcohol Ingestion, Dietary Intake, Serum Antioxidants, Serum Lipids, and Glucose Control

Approximately 8% of adolescents reported that they drank alcohol at least 4 times a month (Table I). Children who reported alcohol consumption at least 4 times a month consumed an average of 4 drinks per drinking episode. Approximately 50% of obese adolescents who reported regular consumption of alcohol (≥4 times per month) had abnormal ALT levels (Table II). In contrast, alcohol consumption by normal weight children had little effect on serum ALT or GGTP levels (Table II). Obese adolescents who reported alcohol intake at least 4 times per month were significantly more likely to have elevations in serum ALT than were obese children who reported drinking less (odds ratio 10.8, 95% CI, 1.5 to 77). In addition, obese children with elevated ALT levels who consumed alcohol regularly had a significantly higher AST/ALT ratio compared with obese children who did not drink alcohol (0.98 ± 0.07 vs 0.68 ± 0.09, $P < .01$). Overall, 92% of obese adolescents who reported regular alcohol consumption were boys. After controlling for alcohol consumption, there was a small, nonsignificant predominance of obese girls

Table IV. Characteristics of overweight and obese adolescents (BMI > 85th%) with and without abnormal ALT levels in NHANES III, 1988-1994

	ALT normal (n = 629)	ALT elevated (n = 45)	*P* value
Dietary intake			
Total energy (kcal)	2177 ± 42	2127 ± 113	.7
Carbohydrate/d (g)	284 ± 6	290 ± 14	.8
Saturated fat/d (g)	28.9 ± 0.6	24.6 ± 2.0	.1
Polyunsaturated fat/d (g)	17.1 ± 0.6	17.5 ± 1.4	.8
Serum lipids and glucose			
Glucose (mg/dL)	88 ± 1	91 ± 2	.2
Glycated Hgb (%)	5.07 ± 0.03	5.27 ± 0.08	<.05
Cholesterol (mg/dL)	167 ± 2	157 ± 4	.05
Triglycerides (mg/dL)*	115 ± 4	141 ± 14	.1
Triglycerides ≥200 mg/dL (%)*	9	23	<.05
Serum antioxidants			
Vitamin C (mmol/L)	45.0 ± 1.3	30.2 ± 4.3	<.01
β-Carotene (μmol/L)	0.21 ± 0.01	0.16 ± 0.01	<.01
α-Tocopherol/lipids (μmol/mmol)*	2.76 ± 0.02	2.34 ± 0.10	<.001

Values are expressed as mean ± SEM. Data from overweight and obese adolescents are combined. Less than 10% of the overweight and obese adolescents reported recent multivitamin use. Overweight and obese adolescents who reported alcohol ingestion ≥4×/month were excluded.
*Values only calculated for fasting levels (>6 hours). ALT normal: n = 508, ALT elevated: n = 41. Similar values of triglycerides and α-tocopherol/lipids were observed in children who fasted >12 hours.

with abnormal ALT levels compared with obese boys (7.9% vs 4.2%, $P = .1$).

No dietary factors other than alcohol intake were related to the presence of abnormal ALT levels in overweight or obese adolescents. Overweight children with or without abnormal ALT levels did not differ in intake of total energy, saturated fat, polyunsaturated fat, or carbohydrate (Table IV).

Overweight and obese adolescents with abnormal ALT levels had significantly lower levels of the serum antioxidants vitamin C, β-carotene, and α-tocopherol compared with overweight adolescents with normal ALT levels (Table IV). Overweight and obese children with elevated ALT levels also had significantly higher levels of glycated hemoglobin ($P < .05$). Overweight children with elevated ALT levels were also significantly more likely to have triglyceride levels >200 mg/dL ($P < .05$). Multivariate regression analysis revealed that only vitamin C levels ($P < 0.05$), α-tocopherol levels ($P < 0.05$), and glycated hemoglobin levels ($P < .05$) were independently correlated with elevated ALT levels in overweight and obese children who did not consume alcohol. However, even after controlling for alcohol intake, serum vitamin C levels, α-tocopherol levels, and glycolated hemoglobin levels, we found that overweight adolescents continued to have an increased risk for high ALT levels compared with normal weight adolescents (odds ratio 2.1, 95% CI, 1.2 to 3.8). In a similar fashion, after alcohol intake, serum vitamin C levels, α-tocopherol levels, and glycolated hemoglobin levels were controlled for, obese adolescents remained at higher risk for increased ALT levels than normal weight adolescents (odds ratio 2.4, 95% CI, 1.1 to 5.0).

DISCUSSION

This study demonstrates that overweight and obesity are the most common causes of elevated liver enzymes in adolescents. Overall, approximately 6% of overweight adolescents and 10% of obese adolescents had abnormal ALT levels. More than 60% of adolescents with elevated liver enzymes without evidence of either hepatitis B or C were overweight or obese. Obese adolescents who drank alcohol on a regular basis were particularly likely to have abnormal liver test results. However, even without alcohol ingestion, obese adolescents were 4 times more likely to have abnormal serum ALT levels than normal weight adolescents.

Nevertheless, the prevalence of abnormal serum ALT levels found in this study was lower than the prevalence found in other studies of obese adolescents. Studies that indicated that 24% to 25% of obese adolescents have elevated serum ALT levels were studies of children referred to obesity centers.[8,20,21] Unfortunately, these studies lacked a reference group of healthy children that would allow researchers to determine the appropriateness of the ALT cutoff value for the population being screened. In addition, obese children referred for specialty treatment are often the most severely overweight (ie, BMI >180% median).

Most obese individuals with elevated ALT values have steatosis without associated inflammatory or fibrotic reac-

tions on liver biopsy.[2,3] Simple steatosis is considered a benign condition with little evidence of progression.[22] However, approximately 30% of obese adults with elevated aminotransferase levels demonstrate steatohepatitis with fibrosis or cirrhosis on liver biopsy,[2,3] and approximately 40% of those patients have progressive liver disease.[23-25] In a similar manner, a report by Kinugasha et al[7] in children suggested that at least 16% of Japanese obese children with elevated aminotransferase levels had fatty liver with associated fibrosis or cirrhosis on liver biopsy. Unfortunately, there is a poor correlation between levels of aminotransferase elevation and liver disease.[7,24,26]

We hypothesize that abnormal liver enzymes in overweight and obese adolescents may result from a combination of hyperinsulinism, hyperlipidemia, and decreased antioxidant levels. We have demonstrated that obese children with abnormal ALT levels had significantly elevated levels of serum glycated hemoglobin and serum triglycerides and significantly lower levels of serum antioxidants compared with obese children with normal ALT levels. Although levels of antioxidants in obese children remained in the "normal range," they were nevertheless substantially lower than those reported in normal weight children.[16] Therefore decreased levels of serum antioxidants observed in obese children may be of sufficient magnitude to increase the risk of oxidative injury.[16] These findings are particularly interesting because preliminary data by Lavine[27] suggest that vitamin E treatment may normalize aminotransferase levels in obese children with steatohepatitis. Unfortunately, fasting serum insulin levels were not measured in adolescents in NHANES III.

The interaction among obesity, alcohol ingestion, and elevated ALT levels in adolescents that we have demonstrated is particularly important because adolescent alcohol ingestion may lead to the rapid development of cirrhosis. Of 53 young adults with cirrhosis under the age of 35 years, 83% began abusing alcohol during adolescence.[28] On pathologic evaluation, NASH and alcoholic steatohepatitis appear identical.[24] It is therefore not surprising that modest alcohol ingestion may exacerbate obesity-associated liver disease. Naveau et al[29] and Braillon et al[2] also demonstrated an increased prevalence of severe hepatic disease in obese adults who consumed alcohol. In addition, animal studies indicate that obesity may potentiate alcohol-induced periportal necrosis in overfed Sprague-Dawley rats through depletion of hepatic antioxidant defenses.[30]

Most obese adolescents in this study with abnormal ALT levels were boys. Although initial reports on adults suggest that abnormal liver histologic characteristics are more common in obese women than in obese men, a later report by Bacon et al[25] found a predominance of NASH in men. Other studies of obese children found a similar pattern of male predominance of liver abnormalities.[6-8] However, these observations were not adjusted for alcohol intake or other possible contributory factors.

Several limitations to this study exist. Liver disease, other than steatosis or steatohepatitis, may be present in obese children with elevated liver enzymes (ie, α-1-antitrypsin deficiency, Wilson's disease, autoimmune hepatitis). However, these other chronic liver disorders are rare and are therefore unlikely to have influenced the results. Unfortunately, the prevalence of gallstones in the obese children was also not assessed. An additional limitation concerns the selection of appropriate cutoff values for serum liver enzymes in children. Unfortunately, no standards exist for abnormal liver enzyme levels in adolescents. The use of an ALT and GGTP cutoff in this study corresponding to the highest 2% of the population is in accordance with standard laboratory procedures. In addition, this study demonstrates that obese adolescents have an increased risk of elevated ALT levels even when higher ALT cutoff values are used.

In summary, these results highlight the fact that the metabolic consequences of obesity begin in childhood. Even though most overweight and obese children with abnormal aminotransferases have only steatosis, those children with persistently elevated aminotransferases may have fibrosis or cirrhosis. In addition, it is important to note that one overweight adolescent and one obese adolescent with elevated ALT levels had antibodies to the hepatitis C virus. Therefore elevations in liver chemistries in obese children should prompt the same evaluations for other causes of chronic liver disease that would be performed in children of normal weight. In particular, Wilson's disease may cause elevations of liver enzymes and steatosis. Adolescents, parents, and physicians also need to be aware that even modest alcohol consumption may significantly increase the likelihood of obese adolescents having steatosis or steatohepatitis. We recommend that comprehensive weight control treatment should be provided for overweight and obese children with evidence of liver abnormalities as soon as possible. In addition, future studies may indicate the usefulness of antioxidant therapy in the treatment of steatohepatitis.

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